

REPORT DOCUMENTATION PAGE

AFRL-SR-AR-TR-02-

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for red Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reductio

0397

1. AGENCY USE ONLY (Leave blank)

2. REPORT DATE

3. REPORT TYPE AND DATES COVERED

21 Oct 02

FINAL REPORT - 01 Apr 02 To 31 Dec 02

4. TITLE AND SUBTITLE

NON-LINEAR DOSE-RESPONSE RELATIONSHIPS IN BIOLOGY,
TOXICOLOGY AND MEDICINE

5. FUNDING NUMBERS

F49620-02-1-0149

2312/AX

6. AUTHOR(S)

Edward J. Calabrese, Ph.D.

61102F

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Massachusetts
Dept. of Environmental Health Sciences
N344 Morrill Science Center
Amherst, MA 01003

8. PERFORMING ORGANIZATION
REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

AFOSR/NL
4015 Wilson Blvd. Room 713
Arlington, VA 22203-1954

10. SPONSORING/MONITORING
AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT

Approve for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

The purpose of the conference was to attract researchers from diverse backgrounds who are working in the common area of non-linear dose-response relationships and to provide a forum to enhance interdisciplinary communication in this area. Outstanding leaders in their respective fields participated in the conference where a variety of important topics were addressed in areas such as pharmacology, toxicology, radiation biology, low-dose modeling, and risk assessment. A poster session was held to promote additional interdisciplinary exchanges and manuscripts have been generated for publication. This unique interdisciplinary conference represents an important step in furthering the understanding of the occurrence, origin, mechanisms, significance and practical applications of non-linear dose-response relationships.

14. SUBJECT TERMS

20021126 065

15. NUMBER OF PAGES

16. PRICE CODE

17. SECURITY CLASSIFICATION
OF REPORT

Unclass

18. SECURITY CLASSIFICATION
OF THIS PAGE

Unclass

19. SECURITY CLASSIFICATION
OF ABSTRACT

Unclass

20. LIMITATION OF ABSTRACT

Walter J. Kozumbo, Ph.D.
AFOSR/NL
4015 Wilson Blvd.
Room 713
Arlington, VA 22203

Re: Final Report (DOD F49620-02-1-0149)

Dear Dr. Kozumbo:

The first International Conference on Non-Linear Dose-Response Relationships in Biology, Toxicology and Medicine was successfully held on June 11-13, 2002 at the University of Massachusetts, Amherst, MA. The purpose of the conference was to attract researchers from diverse backgrounds who are working in the common area of non-linear dose-response relationships and to provide a forum to enhance interdisciplinary communication in this area.

Outstanding leaders in their respective fields participated in the conference where a variety of important topics were addressed in areas such as pharmacology, toxicology, radiation biology, low-dose modeling, and risk assessment (please see the attached conference agenda for the complete listing). A poster session was held to promote additional interdisciplinary exchanges and manuscripts have been generated for publication.

This unique interdisciplinary conference represents an important step in furthering the understanding of the occurrence, origin, mechanisms, significance and practical applications of non-linear dose-response relationships.

Sincerely

Edward J. Calabrese, Ph.D.
Principal Investigator

Department of Environmental Health Sciences
N344 Morrill Science Center
University of Massachusetts
Amherst, MA 01003
Tel: 413-545-3164
Fax: 413-545-4692
email: edwardc@schoolph.umass.edu

21 Oct 02
Zaidar,
Final Report for
AFOSR award to support
Conference in FY2002.
Phase close out -
Walt

**Non-Linear Dose-Response Relationships in Biology,
Toxicology and Medicine
An International Conference**

June 11-13, 2002
University of Massachusetts, Amherst, MA

TUESDAY, JUNE 11, 2002

Morning Session

8:45 Welcome

PLENARY

Moderator: *Paul Kostecki, University of Massachusetts, Amherst, MA*

8:50 **Biphasic Dose Responses in the Biological Sciences**

Edward Calabrese, University of Massachusetts, Amherst

9:30 **Implications of Non-Linearity for Ecological Risk Assessment**

Keith Solomon, University of Guelph, Guelph, Ontario, Canada

10:10 **Break**

10:40 **Evolutionary Foundations of Non-Linearity**

Lorenz Rhomberg, Gradient Corporation, Cambridge, MA

11:20 **Risk Assessment Implications of Non-Linear Dose Responses**

William Greenlee, CIIT, RTP, NC; Frederick Miller, CIIT Centers for Health Research, RTP, NC; Rory Conolly, Center for Computational Biology & Extrapolation Modeling, RTP, NC

LUNCHEON SPEAKER

Reporting on Toxicology and Risk Assessment

Joscelyn Kaiser, Science News Reporter, Science

Afternoon Session

CHEMICAL

Moderator: *John DeSesso, Mitretek Systems, Inc. Falls Church, VA*

1:30 **Complex Shapes of Dose-Response Curves as the Summation of Underlying Low-Dose-Linear and Saturable Processes**

Rory Conolly, CIIT, RTP, NC; David Gaylor, Sciences International, Inc. Little Rock, AR; Kevin Gaido, CIIT, RTP, NC; Werner Lutz, University of Wurzburg, Wurzburg

1:50 **From Mice to Men, Cancers Are Not Certain at Old Age**

Francesco Pompei & Richard Wilson, Harvard University, Cambridge, MA

2:10 **Implications of Hormesis in Developmental Toxicology Risk Assessment**

Mehdi Razzaghi, Bloomsburg University, Bloomsburg, PA

2:30 **Using Dose and Time to Predict Acute and Chronic Toxicity**

Karl Rozman, University of Kansas Medical Center, Kansas City, KS

- 2:50 **Experiences with Non-Linear Dose-Response Relationships in Chemical Evaluations**
Dennis Jones, ATSDR, Atlanta, GA
- 3:10 **Break**
- 3:40 **Risk Modeling Implications of Mechanistic Differences Between Low and High Dose Effects of Arsenic**
Christopher Wells, Tracey Slayton, Barbara Beck & Thomas Lewandowski, Gradient Corporation, Cambridge, MA
- 4:00 **Hormesis, Low-Dose Carcinogenicity and Low-Dose Anti-Carcinogenicity Occur in the Same Animal and With the Same Chemical**
Richard Wilson, Harvard University, Cambridge, MA
- 4:20 **Data for Trichloroethylene-Induced Kidney Tumors in Rodents Suggest an Epigenetic Mechanism of Action**
Amy Levin, International Life Sciences Institute, Washington, DC; Catherine Jacobson & John DeSesso, Mitretek Systems, Inc., Falls Church, VA
- 4:40 **Quantitation of the Dose Response for Formation of DNA Adducts in Rat Liver by 2-Acetylaminofluorene**
Gary Williams, Michael Iatropoulos, Jian-Dong Duan & Alan Jeffrey, NY Medical College, Valhalla, NY
- 5:00 **End**

WEDNESDAY, JUNE 12, 2002

Morning Session

RADIATION

Moderator: *Klaus Becker, Berlin, Germany*

- 8:30 **Impact of Cellular Defense Mechanisms and Bystander Effects on a Multi-Stage Carcinogenesis Model**
Helmut Schollnberger, University of Salzburg, Salzburg, Austria; Margaret Menache, University of New Mexico, Albuquerque, NM; Rod Stewart, PNNL, Richland, WA; Werner Hofmann, University of Salzburg, Salzburg, Austria
- 8:50 **Human Cells Respond to Changes in Background Radiation by Inducing Specific Heat Shock Protein Members**
Satya Saxena, Neeraad Mishra & Stephen Allen, Lovelace Respiratory Research Institute, Albuquerque, NM; Raymond Guilmette, Los Alamos National Laboratory, Los Alamos, NM
- 9:10 **Low-Dose Protective Mechanisms: Implications for Risk Assessment**
Bobby Scott, Dale Walker, Vernon Walker, James Aden & Yohannes Tesfaigzi, Lovelace Respiratory Research Institute, Albuquerque, NM
- 9:30 **Non-Linear Dose-Response Curves in the Immune System Following Whole-Body X-Irradiation**
Shu-Zheng Liu, Norman Bethune University of Medical Sciences, Changchun, China

9:50 **The Hormetic Health Effects of Radiation Observed in the Incident of Co-60 Contaminated Apartments in Taiwan**

Y.C. Luan, M.C. Shieh, S.T. Chen, K.L. Soong & W.K. Wang, Nuclear Science & Technology Association, Taipei, Taiwan, ROC; C.M. Tsai, Atomic Technology Foundation, Taipei, Taiwan, ROC; W.L. Chen, T.S. Chou, S.H. Mong, J.T. Wu & C.P. Sun, NBC Protection Society, Taipei, Taiwan, ROC

10:10 **Break**

10:40 **Dose-Response Relationship: Chromosome Aberrations in Residents at the High Background Radiation Areas in Ramsar, Iran**

S.M. Javad Mortazavi & Takaji Ikushima, Kyoto University of Education, Kyoto, Japan; P. Andrew Karam, University of Rochester, Rochester, NY

11:00 **Residential Radon in US Counties vs Lung Cancer in Women who Predominantly Never Smoked**

K.T. Bogen, Lawrence Livermore National Laboratory, Livermore, CA; J. Cullen, University of California, Berkeley, CA

11:20 **Treatment of Confounding Factors in Ecological Study Test of Linear-No Threshold Theory**

Bernard Cohen, University of Pittsburgh, PA

11:40 **The Bolton-Brush Radiographic Growth Studies**

B. Holly Broadbent & P.S. Rao, Case Western Reserve University, Cleveland, OH

LUNCHEON SPEAKER

Risk Assessment Milestones

John Doull, Department of Pharmacology, Toxicology & Therapeutics, University of Kansas Medical Center

Afternoon Session

ULTRA-LOW DOSES AND MEDICINE

Moderator: Wayne Jonas, Samuelli Institute, Alexandria, VA

1:30 **Effects of Low-Dose Cadmium on Stress Proteins and Survival in Human Prostrate Cells**

Jaya Gaddipati, Rajaesh Kumar, Radha Maheshwari, & Wayne Jonas Uniformed Services University of the Health Sciences, Bethesda, MD; William Achanzar, NCI at NIEHS, RTP, NC

1:55 **Non-Immunological Sensitization: A Nonlinear Host Dose-Response to Repeated Low Level Chemical Exposures**

Iris Bell, The University of Arizona College of Medicine, Tucson, AZ; Carol Baldwin & Gary Schwartz, University of Arizona, Tucson, AZ

2:20 **Ultra-Low Doses and Biological Responses: A Review of the Literature and Recent Experiments**

Wayne Jonas, Samuelli Institute, Alexandria, VA

- 2:45 **High Sensitivity ^1H -NMR Studies of Homeopathic Remedies:
Unexplained Peaks in the Spectra of Some Samples**
David Anick, Harvard University, Cambridge, MA
- 3:10 **Break**
- 3:40 **Challenges to the Investigation of Low and Ultra-Low Dose Effects**
Roeland van Wijk, University of Utrecht, Geldermalsen, The Netherlands
- 4:05 **Low-Dose Effects in Pulmonary Disease**
*Rebecca Bascom, Penn State Milton S. Hershey Medical Center,
Hershey, PA*
- 4:30- **POSTER SESSION**
6:30

THURSDAY, JUNE 13, 2002

Morning Session

BIOMEDICAL

Moderator: *David Diamond, University of South Florida, Tampa, FL*

- 8:00 **Non-Linear Functions Between Stress Hormones, Brain Plasticity
and Memory**
David Diamond, University of South Florida, Tampa, FL
- 8:20 **Biphasic Effects of Progesterone Treatment on Proliferation of
Normal and Malignant Human Ovarian Surface Epithelial Cells**
*Viqar Syed & Shuk-Mei Ho, University of Massachusetts Medical School,
Worcester, MA*
- 8:40 **Two Examples of Paradoxical Pharmacology Using In Vivo Animal
Models of Disease**
*Kenda Evans, Zsuzsanna Callaerts-Vegh & Richard Bond, University of
Houston, Houston, TX; Felix Shardonofsky, Texas Children's Hospital,
Houston, TX; Heather Giles, GlaxoSmithKline, Herfordshire, UK*
- 9:00 **Using *C. elegans* to Model Induced Stress Resistance and Life Span
Hormesis**
James Cypser & Thomas Johnson, University of Colorado, Boulder, CO
- 9:20 **Biological Aging and Its Hormetic Modulation by Repeated Challenge**
Suresh Rattan, University of Aarhus, Aarhus, Denmark
- 9:40 **Hormetic vs Inhibitory Effects in Sea Urchin Bioassays**
Giovanni Pagano, Istituto Nazionale Tumori, Naples, Italy
- 10:00 **Break**
- 10:30 **Non-Linear Factors Affecting Exposure and Risk to Anthrax**
Dennis Jones, ATSDR, Atlanta, GA
- 10:50 **Biphasic Effects of Cardiac Glycosides (Ouabain) on Vascular
Smooth Muscle Cell Proliferation**
*Jullius Allen, Joel Abramowitz & Ashihan Aydemir-Koksoy, Baylor College
of Medicine, Houston, TX*

- 11:10 **Altered Phenotype in Glial Cells Underlies the Low-Dose Neuroprotection Against Neurotoxicity**
Victor Pentreath, University of Salford, Salford, UK; Mark Coodson, Mayo Clinic, Jacksonville, FL; Carole Mead, Christie Hospital, Manchester, UK; Debbie Slamon, AstraZeneca Pharmaceuticals, Cheshire, UK
- 11:30 **Is the Hygiene Hypothesis an Example of Hormesis?**
John Bukowski, ExxonMobil Biomedical Sciences, Inc., Annandale, NJ; Philip Lewis, Rohm and Haas Company, Bristol, PA
- 11:50 **Tissue-Specific Dysfunction Induced by Menthione in Blood Vessels: Mechanisms for U-Shape Dose-Response Curve**
Jin-Ho Chung & Jee-Yeon Han, Seoul National University, Seoul, Korea
- 12:10 Lunch

Afternoon Session

RISK ASSESSMENT

Moderator: *Gary Marchant, Arizona State University, Tempe, AZ*

- 1:30 **Non-Linear Dose Response: Legal Standards for the Admission of Novel Scientific Theories in Regulatory Decision Making**
Gary Marchant, Arizona State University, Tempe, AZ
- 1:50 **Implications of Hormesis for Industrial Hygiene**
Michael Jayjock, Rohm and Haas Company, Spring House, PA; Philip Lewis, Rohm and Haas Company, Bristol, PA
- 2:10 **Do We Need Any Legal Limits for Radon Below About 500 Bq/m³?**
Klaus Becker, Berlin, Germany
- 2:45 **Some Thoughts About How to Incorporate Hormesis Into the Risk Assessment Process**
Brent Finley, Exponent, Santa Rosa, CA; Dennis Paustenbach, Exponent, Menlo Park, CA
- 2:50 **Radiation Hormesis: Molecular-Cellular Biology, Epidemiology, and Prevention and Therapy of Cancer**
Myron Pollycove, North Bethesda, MD; Ludwig Feinendegen, Heinrich-Heine University Duesseldorf, Lindau, Germany
- 3:10 **Basic Research Needs Panel**
Kenneth Mundt, Applied Epidemiology, Inc., Amherst, MA; Wayne Jonas, USUHS, Bethesda, MD; Klaus Becker, Berlin, Germany; Antone Brooks, Washington State University, Richland, WA; Rory Conolly, Center for Computational Biology & Extrapolation Modeling, RTP, NC